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Zinc and skin: an update

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Summary

The essential trace element zinc (Zn) plays a key role in the development, differentiation and growth of various human tissues. Zinc homeostasis is primarily regulated by two zinc transporter families (solute-linked carrier families, SLC). Disturbances in zinc metabolism may give rise to disorders that typically manifest themselves on the skin. An autosomal recessive zinc deficiency disorder, acrodermatitis enteropathica is caused by a mutation in the gene coding for the ZIP_4 transporter. Due to intestinal malabsorption, affected infants develop clinical signs and symptoms shortly after weaning. Acquired zinc deficiency is a rare but underdiagnosed disorder associated with various etiologies and variable clinical manifestations. Depending on the patient's age, a multitude of causes have to be considered. Given the characteristic periorificial and acral lesions, the clinical diagnosis is usually made by dermatologists. Laboratory confirmation includes measurement of plasma zinc levels and – as a supplementary measure – zinc-dependent enzymes such as alkaline phosphatase. Oral zinc replacement therapy frequently leads to clinical remission within a few days. Depending on the cause, disease management should include cooperation with pediatricians and gastroenterologists in order to guarantee optimal patient care.

Introduction

The essential trace element zinc plays a key role in the development and maintenance of all tissues, including the skin in particular [1]. The human body physiologically contains a total of 2–3 grams of zinc [2]. Zinc homeostasis is regulated by two zinc transporter families (solute-linked carrier families, SLC): the zinc transporters ZnT, encoded by the genes *SLC30A1* to *SLC30A10*, and the *Zrt- and Irt-like protein transporters* ZIP, encoded by the genes *SLC39A1* to *SLC39A14* [3, 4]. ZnT and ZIP transport zinc in opposite directions. ZIP increase zinc levels in the cytosol, whereas ZnT mediate zinc transport from the cytosol into extracellular or other intracellular compartments. Apart from the zinc transporters ZnT and ZIP, small cytosolic proteins – called metallothioneins – also play an important part in cytosolic zinc homeostasis. Given their ability to bind to heavy metals (such as zinc), these proteins regulate zinc levels by binding or releasing it on an as-needed basis [5].

Dietary zinc is absorbed in the small intestine through the specific zinc transporter ZIP4 and is then released into the bloodstream by zinc transporters such as ZnT-1 [4]. Intestinal zinc absorption is inhibited by dietary fiber and phytic acid [6]. A major portion of the absorbed zinc is bound to albumin, transported to the liver and eventually stored in muscles and bones (80–85 %) as well as in the skin and liver (8–11 %) [4]. The amount of zinc we can measure – in serum or plasma – is therefore only a fraction of the total zinc present in the body. Physiologically, we lose roughly 2–4 mg of zinc daily through the gastrointestinal tract and about 0.5 mg through the kidneys. In addition, there is physiological loss of zinc through the skin and hairs [7].

Zinc plays a crucial role in the development, differentiation and cell growth of many tissues, as it is a cofactor for more than 1,000 enzymatic reactions and more than 2,000 transcription factors [2, 8]. In epidermal keratinocytes, zinc is substantially involved in their differentiation as well as anti-inflammatory and wound healing processes [8]. At 60 µg/g, the concentration of zinc is much higher in the epidermis than in the dermis and subcutis [9]. The zinc transporter ZIP2 as well as metallothioneins are instrumental in supplying keratinocytes with zinc. It has been shown in a mouse model that zinc deficiency may lead to loss of Langerhans cells in the epidermis. Usually, epidermal Langerhans

cells hydrolyze adenosine triphosphate (ATP) secreted by keratinocytes into adenosine monophosphate (AMP). Consequently, zinc deficiency in keratinocytes can result in local excess of ATP in the epidermis, and thus to ATP-mediated inflammation of the skin with characteristic lesions [8]. Zinc deficiency is associated with numerous effects on the immune system [10], such as impairment of maturation and function of T and B lymphocytes and alterations in the balance between Th1 and Th2 immune responses as well as between regulatory and proinflammatory T cells. Th17 immune responses are promoted by zinc deficiency; the activity of NK cells is decreased. Zinc deficiency also plays a crucial role in innate immunity. The production of cytokines and reactive oxygen species, which are both required in the defense against pathogenic microorganisms, may also be impaired in individuals with zinc deficiency.

Irrespective of its cause, zinc deficiency clinically presents with the classic triad of dermatitis, alopecia and diarrhea [11]. The present review highlights the various causes and clinical features as well as the diagnosis and treatment of zinc deficiency dermatitis.

Epidemiology

Acquired zinc deficiency currently affects about 17 % of the population worldwide [12]. In developing countries in particular, zinc deficiency is associated with an increase in morbidity and mortality among many children [13]. In addition, preterm infants, elderly individuals and pregnant women are at risk worldwide [2, 13, 14]. In Germany and other industrial nations, risk populations for acquired zinc deficiency include vegetarians, alcoholics, malnourished individuals and preterm infants [1]. The incidence of hereditary acrodermatitis enteropathica (AE) is approximately 1–5/500,000 [15].

Etiology

Zinc deficiency can have various causes. Corbo et al. have proposed a classification into four different types, based on the underlying etiology [16] (Table 1).

Insufficient zinc supply (type I) in infants and children is usually caused by parenteral nutrition, undernourishment, malnutrition or low zinc levels in breast milk [7]. Transient neonatal zinc deficiency (TNZD) may be caused by a mutation in the mother's *SLC30A2* gene, which encodes the zinc transporter ZnT2 [17]. Furthermore, eating disorders such as anorexia nervosa and bulimia as well as alternative eating habits (vegetarianism, veganism) can lead to zinc deficiency not only in children and adolescents but also in adults [18].

Excessive loss of zinc (type II) may result from disorders of the gastrointestinal or urinary tract [19].

The large group of malabsorption disorders (type III) that cause zinc deficiency includes chronic inflammatory

Table 1 Etiology of zinc deficiency (modified after [16]).

Insufficient intake (type I)	Increased loss (type II)	Malabsorption (type III)	Increased requirement (type IV)
▸ *Infants*: – Low serum zinc levels in breastfeeding women – Low zinc levels in breast milk ▸ Parenteral nutrition ▸ Certain diets ▸ Anorexia nervosa ▸ Bulimia	▸ *Gastrointestinal causes*: – Recalcitrant diarrhea – Intestinal fistulas ▸ *Urine*: – Liver cirrhosis – Infections – Renal diseases – Diabetes mellitus – Alcohol – Diuretics ▸ Burns ▸ Excessive sweating ▸ Hemodialysis ▸ Hemolysis	▸ *Hereditary*: – Acrodermatitis enteropathica – Cystic fibrosis ▸ *Gastrointestinal causes*: – Crohn's disease – Ulcerative colitis – Celiac disease – Short bowel syndrome, irritable bowel syndrome – Diseases of the liver and pancreas ▸ *Drugs*: – Penicillamine – Diuretics – Valproate ▸ High intake of phytic acid/copper/iron ▸ Bariatric surgery	▸ Pregnancy ▸ Breastfeeding ▸ Preterm babies ▸ Elderly individuals

bowel diseases like Crohn's disease and ulcerative colitis, as well as celiac disease, short bowel syndrome and AE [19]. Cystic fibrosis, the second most common hereditary metabolic disease, may also cause zinc deficiency [19]. In addition, high intake of copper, iron or phytic acid can lead to malabsorption of dietary zinc [20]. Gastrointestinal or bariatric surgery (e.g., gastric banding, partial resection of the stomach, gastric bypass) decreases the absorption of food and nutrients and are thus also associated with an increased risk of zinc deficiency [21]. As a consequence, it is recommended that such procedures are followed by close postoperative monitoring as well as supplementation of various micronutrients (trace elements and vitamins) such as zinc [7].

Increased zinc requirement (type IV) is commonly seen during pregnancy and breastfeeding.

Clinical features

Given the various functions zinc has in the human body, the clinical presentation of manifest zinc deficiency can be very diverse (Table 2). The typical triad of periorificial dermatitis, alopecia and diarrhea is frequently accompanied by other, less specific symptoms such as impaired wound healing, disorders of the gustatory (dysgeusia) or olfactory (dysosmia) sense [7], night blindness and/or immunodeficiency. Affected patients more commonly develop bacterial and fungal infections, not only of the skin. This is likely attributable to zinc-mediated effects on certain leukocyte functions [22]. Affected children also exhibit failure to thrive and growth retardation [4].

Cutaneous manifestations of zinc deficiency consist of sharply demarcated eczematous or psoriasiform plaques, frequently with peripheral scaling and crusts. Subsequently, vesicles or pustules may appear [1]. The lesions typically occur in acral and periorificial areas and in the anogenital region; they are therefore referred to as acral, pluriorificial dermatitis. Without proper treatment, extensive erosions associated with a predisposition for fungal (e.g. *Candida albicans*) or bacterial (e.g. *Staphylococcus aureus*) colonization may ensue, as well as severe diffuse alopecia.

Table 2 Clinical signs and symptoms of zinc deficiency.

Organ system	Signs and symptoms
Skin and skin appendages	Acral and pluriorificial dermatitis, alopecia, paronychia, impaired wound healing, glossitis, cheilitis
Gastrointestinal system	Diarrhea, dysgeusia
Central nervous system	Dysosmia, cognitive impairment, night blindness
Immune system	Increased incidence of bacterial, fungal and viral infections

Acrodermatitis enteropathica (AE) and transient neonatal zinc deficiency (TNZD)

Being a rare autosomal recessive disorder, AE was first described by Brandt et al. in 1936 [23]. In the mid-20th century, Niels Danbolt and Karl Closs in particular characterized the disease in more detail [3, 24, 25]. The causal relationship between zinc deficiency and AE was pointed out by Barnes et al. and Moynahan et al. [26, 27] in 1973 and 1974. Finally, an intestinal enzyme defect was identified as the possible cause leading to zinc deficiency [28, 29]. It was not before 2002 that *loss-of-function* mutations in the *SLC39A4* gene, which codes for the zinc transporter ZIP4, were eventually identified [30, 31]. By now, there are roughly 34 known mutations that affect the function of the intestinal ZIP4 transporter (16 missense, 4 nonsense, 3 splice-site and 11 frameshift mutations) [17].

The classic triad of perioral, intertriginous and acral dermatitis (Figure 1), alopecia and diarrhea only occurs in roughly one-third of the patients [3, 11]. First signs and symptoms usually appear shortly after weaning. The likely cause for this temporal correlation is that zinc is more bioavailable in human milk compared to cow's milk. Unlike this phenomenon, patients with TNZD show initial clinical manifestations already during breastfeeding (Figure 2). Breast milk usually contains adequate amounts of zinc for infants up to the age of about six months. In TNZD, however, a mutation in the mother's *SLC30A2* gene results in impaired function of the zinc transporter ZnT2 [32], thus leading to low zinc levels in the breast milk and subsequent zinc deficiency in the breastfed infant (Table 3).

Acquired zinc deficiency

A large part of the medical literature on zinc deficiency covers the rare hereditary form of AE and its manifestations in infants. However, acquired zinc deficiency, which presents with comparable signs and symptoms, is substantially more common [33]. Various reports of cases with different etiologies describe similar cutaneous manifestations of acquired zinc deficiency. Acquired zinc deficiency too predominantly presents with well-delineated, erythematous, sometimes scaly and crusted plaques and erosions [33]. Similar to hereditary zinc deficiency, the typical lesions primarily occur in acral and periorificial areas as well as intertriginous regions (Figure 3).

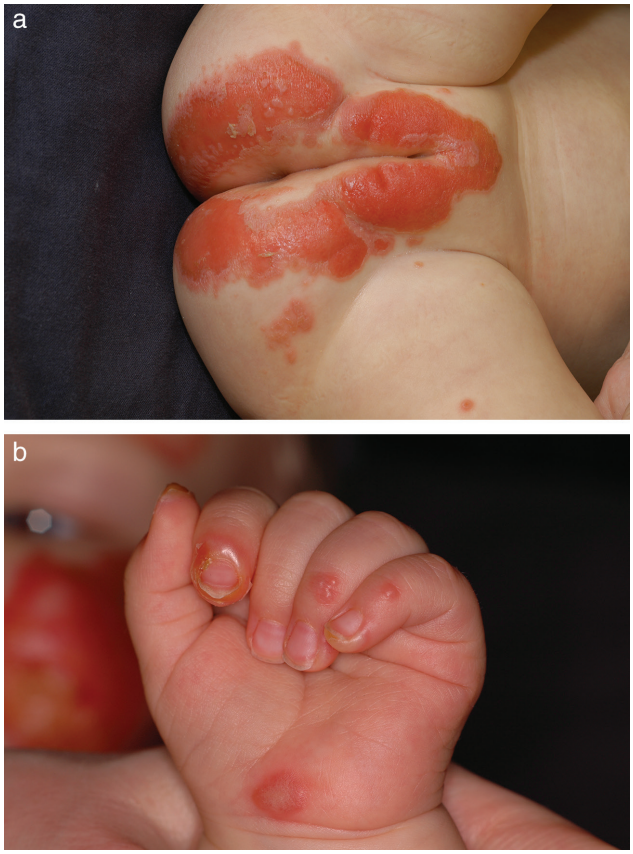

Figure 1 10-month-old infant with acrodermatitis enteropathica. Sharply demarcated, erosive erythematous plaques in the anogenital region (a) and in acral areas (b).

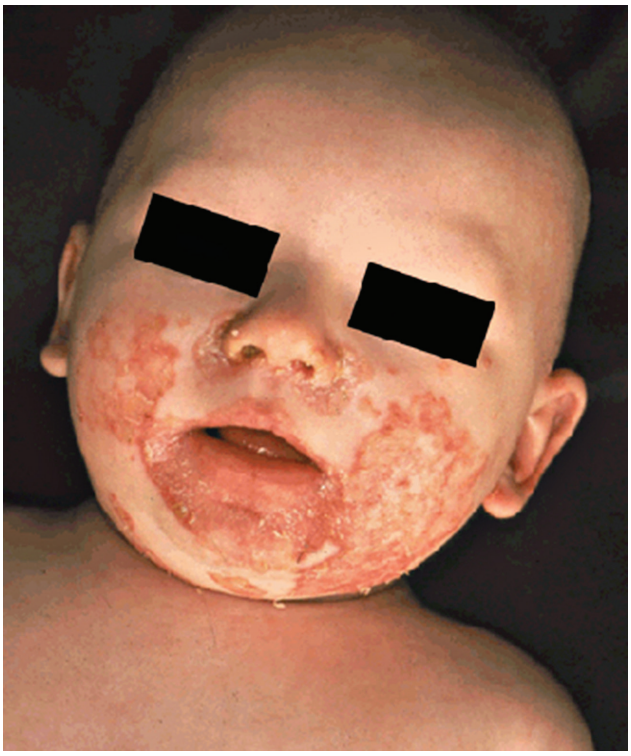

Figure 2 5-month-old infant with transient neonatal zinc deficiency. Erythematous crusted periorificial plaques (from Leverkus et al. [34], reproduced with permission by the publisher [Wiley]).

Other concurrent findings commonly seen include hair loss or alopecia, paronychia, glossitis or cheilitis [34, 35].

Differential diagnoses

Differential diagnostic considerations in infants and children must include the large group of rare metabolic diseases. On dietary treatment, a number of these disorders (Table 4) can cause skin lesions that resemble AE [36] and are referred to as acrodermatitis dysmetabolica [37] or acrodermatitis acidemica [38]. For instance, patients with the rare, autosomal recessive maple syrup urine disease may develop periorificial and acral skin lesions on dietary treatment, likely due to isoleucine deficiency [36]. Another rare but important differential diagnosis of zinc deficiency presenting with skin lesions is methylmalonic acidemia (MMA) [39], a group of autosomal recessive hereditary diseases characterized by defects in amino acid metabolism [40]. There are other rare metabolic

Table 3 Characteristics of acrodermatitis enteropathica (AE) and transient neonatal zinc deficiency (TNZD).

	AE	TNZD
Onset	After weaning	During breastfeeding
Zinc levels in serum	Low	Low
Zinc levels in breast milk	Normal	Low
Genetic cause	Mutation in the child's *SLC39A4* gene, which encodes the ZIP4 zinc transporter	Mutation in the mother's *SLC30A2* gene, which encodes the ZnT2 zinc transporter

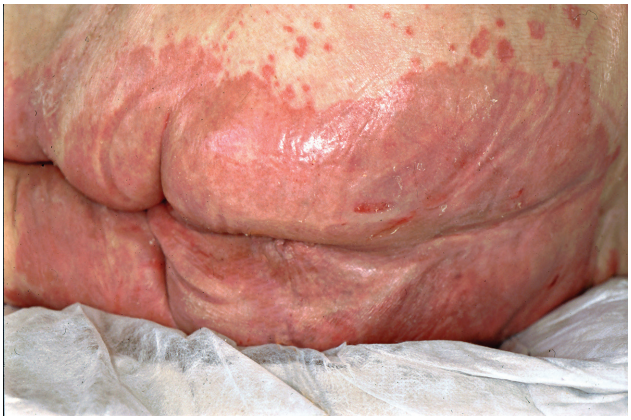

Figure 3 93-year-old female patient with acquired zinc deficiency. Large, sharply demarcated, erythematous, oozing plaques with satellite lesions in the lumbosacral and gluteal region and on the dorsal aspects of the thighs.

disorders, such as citrullinemia or necrolytic migratory erythema (glucagonoma syndrome), that are associated with similar skin lesions [37, 38]. Important differential diagnoses in adults include seborrheic dermatitis, impetiginized dermatitis, psoriasis and fungal (candidal) infections [1].

Wound healing

Given that many zinc-dependent molecules are involved in the complex process of wound healing [41], it is safe to assume that this trace element plays a key role [42]. Delayed wound healing has primarily been described in patients with zinc deficiency [41]. While topical application of zinc paste has been shown to facilitate wound healing [43], it is still a matter of debate whether oral zinc supplementation is beneficial in this regard in patients without zinc deficiency [42]. A systematic review of six small-scale studies found no evidence of improved wound healing with oral zinc supplementation [44]. Larger, controlled trials are necessary to assess the potential benefits of topical zinc application and oral zinc supplementation for the treatment of chronic wounds in patients without manifest zinc deficiency.

Table 4 Rare metabolic diseases presenting with skin lesions reminiscent of zinc deficiency (modified after [37]).

Metabolic diseases
Maple syrup urine disease
Methylmalonic acidemia
Urea cycle disturbances (citrullinemia, ornithine transcarbamylase deficiency, carbamoyl phosphate synthetase I deficiency)
Glucagonoma syndrome (necrolytic migratory erythema)
Phenylketonuria
Glutaric aciduria type I
Propionic acidemia
Biotin deficiency

Zinc and hair

Although zinc plays a major role in the keratinization of hair, the underlying mechanism is as yet unknown [8]. Zinc deficiency can lead to delayed hair growth, loss of pigmentation, and thinning/caliber variations of hair shafts, both in AE and in acquired forms of zinc deficiency [22]; as a consequence, the scalp hair looks dry and brittle. Similar to sulfur deficiency (trichothiodystrophy), irregular bands can be observed in the hair shafts on polarization microscopy [45]. While telogen hair loss can lead to – occasionally severe – diffuse alopecia, this condition can be effectively remedied by oral zinc supplementation. There is, however, no evidence that zinc supplementation has any benefits in terms of hair growth in individuals with normal zinc levels.

Diagnosis

A systematic review from 2009 concluded that lab tests measuring plasma zinc levels are fairly reliable in detecting zinc deficiency [46]. However, low zinc levels in plasma or serum do not necessarily indicate zinc deficiency; on the other hand, zinc deficiency dermatitis (that improves with zinc replacement therapy) is seen in patients with normal zinc levels [1]. Thus, zinc levels in plasma or serum have only limited value as biomarkers of zinc deficiency [47]. This is mainly due to the fact that plasma zinc comprises only 0.1 % of the total amount of zinc in the body [1]. While the diagnosis of zinc deficiency can still be made based on measuring zinc levels in plasma or serum, it is important to keep in mind the comparatively low sensitivity of this lab test. Fasting zinc levels of less than 70 µg/dL (10.71 µmol/L) or post-meal levels of less than 65 µg/dL (9.95 µmol/L) [6] are therefore indicative but not proof of zinc deficiency. In routine practice, zinc levels in plasma and serum are considered to be equivalent. Normal values in plasma range between 70 and 110 µg/dL (10.71–16.83 µmol/L); in serum, between 80 and 120 µg/dL (12.24–18.36 µmol/L) [48]. In addition, zinc-dependent enzymes, such as alkaline phosphatase, can be measured as surrogate markers [16]; the latter is frequently decreased in patients with zinc deficiency. For diagnosing insufficient zinc intake, it may be useful to measure the serum zinc binding capacity, which will often be increased [49]. Blood should be drawn in the morning using a stainless steel needle and a

vial free of trace elements [6]. When interpreting the results, one must bear in mind that plasma zinc levels (due to a shift of zinc into the cells) may be decreased in an acute-phase reaction without affecting body zinc stores [7]. Given that zinc is bound to albumin, hypoalbuminemia may mimic zinc deficiency due to decreased zinc binding capacity; a similar effect can be seen in hemodilution. In such cases, low zinc levels should therefore be interpreted with caution and always be correlated with the patient's clinical presentation.

While it is possible to measure zinc levels in urine, this test is diagnostically less conclusive [48]. One would expect that zinc deficiency is associated with a decrease in urine zinc levels (compensatory reaction). However, increased zinc concentrations in urine can also be caused by urinary loss of zinc and therefore indicate zinc deficiency [7]. Reference values for urinary zinc excretion are 4.5–9.0 µmol/L (0.3–0.6 mg) per day [50].

Measuring hair zinc concentrations is less suitable for diagnosing acute zinc deficiency, as this is only an indication of long-term zinc metabolism [22].

Histology

Histological findings in zinc deficiency dermatitis are nonspecific and usually indistinguishable from other types of "deficiency dermatitis" (e.g. pellagra) or cutaneous manifestations of various metabolic diseases (e.g. necrolytic migratory erythema) [1]; histology is primarily used to rule out other disorders. Initially, zinc deficiency dermatosis is characterized by alternating orthokeratosis and parakeratosis. Subsequent findings include confluent parakeratosis, decreased stratum granulosum as well as acanthosis and focal acantholysis. Dermal capillaries are dilated, and there is a sparse lymphohistiocytic infiltrate in the papillary dermis. Later stages are marked by ballooning degeneration of keratinocytes with a pale cytoplasm (necrolysis). Chronic lesions sometimes show a psoriasiform pattern [16]. Histologically, psoriasis can be distinguished by the lack of necrotic keratinocytes and the presence of neutrophils in the epidermis.

Treatment

The reference values for optimum zinc intake per day (according to the *UK reference nutrient intake*) are about 9.5 mg for adult men and 7.0 mg for adult women [51]. The requirements are higher in infants, children, pregnant and breastfeeding women and elderly individuals [7]. Treatment of zinc deficiency is determined by the cause of the disorder. Patients with hereditary AE should take elemental zinc (Zn^{2+}) at a dose of 3 mg/kg per day. As a supplementary measure, plasma or serum zinc levels should be measured every 3–6 months, and the dosage adjusted accordingly [1]. For patients with acquired zinc deficiency, elemental zinc (Zn^{2+}) at a dose of 0.5–1 mg/kg per day is usually sufficient to resolve the deficiency [1]. Various zinc supplements are commercially available, both inorganic zinc salts, such as zinc sulfate and zinc chloride, and organic preparations such as zinc histidinate, zinc gluconate and zinc orotate. Organic compounds show a comparatively better tolerability [22]. The dose should be adjusted based on the content of elemental zinc in the respective product – e.g., 220 mg of zinc sulfate contains about 55 mg of Zn^{2+}. Approximately 70 % of patients respond successfully to replacement therapy within the first six months after treatment initiation [19]; frequently, clinical improvement can be observed after just a few days [52]. The duration of treatment also depends on the etiology of the zinc deficiency. Patients with reversible zinc deficiency usually require supplementation for 3–4 months [19], whereas those with hereditary AE require lifelong replacement therapy. Because of possible interactions, copper and iron levels should also be monitored on a regular basis [16]. Zinc replacement therapy may be associated with undesired adverse effects, including diarrhea, nausea, vomiting, mild headaches and fatigue [1].

Conclusion

In developed countries, zinc deficiency dermatitis is comparatively uncommon. However, zinc deficiency should be considered and appropriately worked up in patients presenting with typical skin lesions, particularly in risk populations. Depending on the underlying disease, patient management should ideally include the cooperation with pediatricians and gastroenterologists.

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